

The cost-effectiveness of EndoPredict to inform adjuvant chemotherapy decisions in early breast cancer

Article (Accepted Version)

Hinde, Sebastian, Theriou, Chloi, May, Shirley, Matthews, Lucy, Arbon, Amy, Fallowfield, Lesley and Bloomfield, David (2019) The cost-effectiveness of EndoPredict to inform adjuvant chemotherapy decisions in early breast cancer. *Health Policy and Technology*, 8 (1). pp. 75-83. ISSN 2211-8837

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The Cost-Effectiveness of EndoPredict to Inform Adjuvant Chemotherapy Decisions in Early Breast Cancer

Abstract

Background

Adjuvant chemotherapy in breast cancer patients post resection has been estimated to reduce mortality rates by up to 30%. However, the heterogeneous nature of the disease and patients implies that not all patients should receive the treatment. Many existing prognostic tools, may not definitively estimate the most effective treatment strategy, resulting in an *indeterminate* risk classification. In such cases gene expression profiling tests can aid the treatment decision.

Methods

This study evaluated the cost-effectiveness of EndoPredict in patients with indeterminate risk classification. A mathematical model was constructed to determine how the change in treatment decisions impacted the long term health of the population, and the future cost implications to the NHS.

Results

EndoPredict was found to lead to 36.9% of patients having a change in treatment decision. As a result its use was found to result in an increase in population health but also in total costs, resulting in an incremental cost-effectiveness ratio of £26,836 per quality adjusted life year. This was subject to significant parametric and structural uncertainty.

Conclusion

While EndoPredict was found to be more expensive overall, its ability to affect a more optimal allocation of chemotherapy, resulted in long term health gains, however, they were insufficient to justify the high cost of EndoPredict.

Introduction

Breast cancer is one of the most common types of cancer in women. In the UK 30% of all cancer patients and about 42,489 female patients are diagnosed with breast cancer every year.[1] In early-stage breast cancer, patients undergo surgery (mastectomy or lumpectomy) to remove the primary cancer. However, there is a risk that some cells may have left the primary tumour before removal and spread to other parts of the body as micro- metastases. The risk of metastatic disease, and death from breast cancer can be reduced with systemic adjuvant therapy. The majority of breast cancers are hormone sensitive (oestrogen receptor (ER) +ve) and there will be clear benefit from tablet based anti-hormonal treatment such as tamoxifen or an aromatase inhibitor. Furthermore, systemic anti-cancer chemotherapy can be added to the treatment regimen to attempt to directly target residual microscopic metastases and lower the risk of the cancer returning. According to the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), post-operative chemotherapy can reduce mortality rates by approximately 30% in ER +ve patients.[2]

Despite the strong evidence of a reduced risk of disease recurrence with chemotherapy treatment, the heterogeneous nature of both the disease and the patients treated requires the consideration of the patient specific risk of recurrence of the cancer. Patients at high risk of recurrence would be expected to benefit significantly from chemotherapy, while those at low risk unlikely to benefit. This study focuses on the patients whose risk falls between the clearly high and low risk patients, those deemed of intermediate risk of recurrence using conventional risk estimation approaches, and thus in whom the decision to provide chemotherapy or not is most challenging.

Tools with which to estimate the risk profile of future disease recurrence can be broadly categorised as gene and non-gene informed prognostic tools, where examples of gene informed tools include Oncotype DX and EndoPredict and non-gene informed the Nottingham Prognostic Index [NPI], and PREDICT. Recent NICE guidance[3] considered the use of gene expression profiling alongside conventional risk tools, recommending the use of Oncotype DX in patients assessed as being at intermediate risk by non-gene informed tools, but recommending against the other gene informed tools assessed (MammaPrint, IHC4 and Mammostrat). The subsequent entry to market of EndoPredict and Prosigna resulted in NICE issuing a Medtech Innovation Briefings (MIB44 and MIB27 both in 2015),[4, 5] a means by which NICE provide guidance on the new technologies but not a robust recommendation. As such, EndoPredict has currently no formal NICE recommendation status, and as the Briefing demonstrated, only limited clinical or economic evidence. An updated NICE Guidance is currently being produced.[6]

In this manuscript we present the findings of an economic analysis of a trial into the use of EndoPredict, through this we hope to aid decision making of patients with an initial intermediate risk score using standard risk tools, considering both the potential for short term cost saving and long term cost effectiveness.

Methods

The trial

Details of the trial on which this analysis is based are provided elsewhere[7] but in brief, it is a small scale (n=149 patients), manufacturer sponsored (an unrestricted educational grant from Myriad Genetics) study of EndoPredict, a validated multigene test which provides additional prognostic information to the risk of distant recurrence of breast cancer patients, independent of clinic-pathologic parameters[8]. The EndoPredict score is combined with two clinical parameters, nodal status and tumour size, resulting in a hybrid molecular-clinico-pathologic prognostic score (EPclin), we will use the term EndoPredict to reflect the use of the initial score and clinical parameters.[9, 10]

The trial was conducted across eight sites in the south-east of England. Between July 2015 and September 2016 women at each site were eligible for inclusion if they were the first presentation of early breast cancer with all known disease surgically removed, Oestrogen Receptor +ve and HER-2 negative, with no clear decision on whether chemotherapy should be given as adjunct based on current prognostic criteria as preferred by the clinical team (e.g. an intermediate Nottingham Prognostic Index risk/PREDICT benefit). The mean age of patients was 56.5, with a range of 25.9 to 77.2. Of the 149, 19 (13%) were diagnosed with Grade I, 87 (57%) Grade II, and 43 (29%) Grade III cancer. Both nodal positive (n=141) and negative (n=8) patients were included, a histogram of the number of nodes involved in included in the supplementary appendix.

With their oncologist, patients identified as being in the intermediate risk group came to a provisional treatment decision regarding the use of chemotherapy, and if so relevant regimen, dose and cycle length, using standard clinical-pathological criteria constituting the standard practice of the oncologist. This could include the use of online prognostic tools including PREDICT and Adjuvant! Online (which was offline for most of the trial period). This decision was recorded prior to patients being consented for the trial. If the patients consented a tissue sample was sent for EndoPredict testing prior to re-consultation within two weeks, at which point the results were discussed and an updated treatment regimen decided. No trial follow up was planned beyond the second consultation, as such the primary outcome is the impact of EndoPredict to change the initial treatment decision.

Analytical Overview

This economic analysis consists of a two-step evaluation. First, we investigate whether the addition of EndoPredict increases or decreases the use and intensity of chemotherapy in the trial population, and the associated direct cost implications to the NHS. Secondly, in order to conceptualise the potential long-term cost and health related implications of the test, a mathematical model is constructed. The analysis takes the perspective of the NHS, such that only the costs directly incurred by the NHS are included. The primary outcome of interest in patient health, estimated through quality adjusted life years (QALYs). QALYs are discounted at a rate of 3.5% per annum, consistent with standard methods.[11]

Cost are measured in 2016 Pound Sterling, and future costs and benefits are discounted at a rate of 3.5% per annum. Where costs are drawn from sources before 2016 they are inflated using the Hospital and Community Health Services (HCHS) index.[12] Where available evidence from the trial was used to inform micro-costing analysis, for example with chemotherapy costs, if no such evidence was available evidence from the wider literature and reference cost resources were used.

Uncertainty is conceptualised in the analyses through the use of probabilistic sensitivity analysis (PSA), conducted over 3,000 iterations. The PSA analysis draws from informative distributions of all of the key model parameters, including the impact of the addition of EndoPredict to the treatment decision, the model transitions, costs, and patient related quality of life, the informative distributions are detailed in Table 1.

The long term analysis results include estimates of the incremental costs, QALYs, and net monetary benefit (NMB), in addition to the results of the PSA, estimating the probability of EndoPredict being a cost-effective intervention relative to standard decision criteria only. Value of information analysis is conducted to estimate the consequences of an incorrect decision. Additionally, a scenario analysis is conducted to explore the potential impact of the proportion of patients who receive treatment that deviates from the EndoPredict risk score, for example a patient who has an EPclin high score reported but did not received chemotherapy.

Chemotherapy cost analysis

This analysis considers both the proportion of patients receiving chemotherapy with and without EndoPredict as well as the intensity and type of chemotherapy prescribed. The analysis considers the direct costs to the NHS of the treatment regimens to determine the impact of EndoPredict on the cost of chemotherapy treatment, using an intention to treat approach. Due to the lack of

patient follow up in the trial only the acquisition and provision of the prescribed treatments, and the cost of EndoPredict are estimated, the subsequent cost implications of adverse events and increased care are incorporated in the long term extension detailed in the next section. The cost of each regimen is estimated at a patient level from the trial data, both before and after the EndoPredict decision, which are used to represent two arms of the decision problem. For the cost analysis details on the selected regimen, dose, number of cycles, and body surface area (estimated using the Mosteller formula) are combined with the unit cost of each regimen, drawn from the British National Formulary (BNF)[13] and the estimated laboratory and human resource costs of delivery, applied as a fixed cost per cycle of £139.39.[14] To reduce the impact of intra-site variation regimen dose was standardised to the lead site's approach, the analysis takes the lowest cost of each chemotherapy drug from the BNF, assuming perfect divisibility of vials with no waste. Only the costs of chemotherapy treatment is included in the analysis due to the low cost and high degree of variation in reporting of endocrine therapies in the trial.

To consider the full short term cost of the use of EndoPredict its cost is also factored in to this analysis. The cost of EndoPredict is drawn from the NICE briefing[4] which reported a cost of £1,500.

After standardisation and cleaning of the trial data three cases of missing drug dose were detected, these were imputed using the mean dose of other patients receiving that drug. Three cases of missing height and weight were detected (required for body surface area), which were imputed as an unadjusted average from the rest of the trial patients. Two patients were detected as having a decision of chemotherapy but with no named drugs in the regimen, these patients had the average cost across matched treatment decisions imputed. Finally, two patients who were enrolled in the trial but did not have EndoPredict conducted were dropped from the analysis, leaving 149 patients.

The long term mathematical model

As part of this analysis a systematic search of the literature was conducted, the search strategy for which is provided in the Supplementary Appendix. It found no existing evaluative models suited to the required long term analysis, with the only previous economic analysis of EndoPredict that by Blank in 2014.[9] While the Blank study is informative, and is used to guide several of the model parameter values, as it was conducted from a German perspective without focus on the intermediate risk group, it was not considered directly comparable with this analysis. This conclusion is consistent with the review of the literature conducted by NICE for the EndoPredict Briefing.[4] As a result, a de novo mathematical model was constructed with which to compare the long-term costs and benefits associated with a cohort of patients assessed using standard decision criteria of the treating oncologist, compared to standard decision criteria plus EndoPredict.

The model represents a decision tree leading to a three state Markov cohort analysis with a lifetime timeframe and an annual cycle length. The Markov model includes three disease states modelled (disease-free, recurrent disease, and death), and the decision tree divides patients into one of four groups determined by their EndoPredict risk categorisation and treatment decision: EPclin low + chemotherapy, EPclin low + no chemotherapy, EPclin high + chemotherapy, and EP clin high + no chemotherapy. The modelled base-case population selected was done so to matches the average patient from the trial which we believe reflects the real world population well in this setting, being a cohort of 56 year old women who were diagnosed with oestrogen receptor-positive, human epidermal growth factor receptor 2 negative (ER+/HER2-) early breast cancer, having had an intermediate risk score using the standard risk tool. The model structure is presented in Figure 1.

[Figure 1 here]

Parameter Values

EndoPredict and treatment classification

As presented in the model schematic (Figure 1), the population is divided into four risk and treatment populations for both the arm that had access to EndoPredict or used a standard decision making process only. The chemotherapy decisions made in the 'No EndoPredict' arm is informed by the decisions made by the clinician and patient prior to the use of EndoPredict in the trial, and as such is assumed to represent the treatment decision that would result from the standard decision making process indicative of current NHS practice. Similarly, the chemotherapy decisions represented in the 'EndoPredict' arm of the model are the updated decisions made in the trial after the estimation of the EndoPredict risk score. The proportion of patients in each of the four populations is estimated directly from the trial results, reported in Table 1.

Transition probabilities

Prior to entering the Markov part of the model, all patients on a chemotherapy regimen have the potential of dying due to related toxicity. This probability is estimated from a study by Campbell.[15] The Markov model's three state structure allows patients to transition from each state to any which represents a worsening health state (i.e. disease free to metastases, disease free to death, metastases to death).

The EPclin score and treatment decision associated with a patient is assumed to only effect the transition probabilities from the initial disease free state to metastases. Both factors are considered as independent factors affecting the expected probability of a patient experiencing disease

metastases, the estimates and sources of these effects are shown in Table 1. The annual probability of metastases for the 10 years after surgery for patients receiving no chemotherapy is estimated from the study by Blank,[9] stratified by EPclin score. The published Kaplan-Meier curves for metastatic free survival were digitised (using Engauge[16]) and an exponential hazard function fitted (chosen due to the findings of Blank that this functions provide the best fit to the data). The progression free survival curves were then adjusted by the mortality rate of the population to yield the required metastases rate, associated standard errors were estimated to inform the PSA analysis.

For the patients who receive chemotherapy a treatment effect is applied to the disease free to progressed transition probability. Consistent with Blank[9] a treatment effect of 0.69 (SE 0.04) is used which is independent of the risk status of the patients.

10 years after surgery all patients still in the disease free state are assumed to be 'cured' of the original disease due to the inability of our model to differentiate cancers which occur after this time point with the initially treated cancer rather than a newly occurring one, and as such are no longer able to transit to a state of disease metastases, only to death from unrelated causes. The impact of this assumption is expected to be minimal as the death from 'unrelated causes' will include potential long term recurrences.

The transition probabilities governing mortality, from the disease free and progressed states were informed by two sources. Death not related to breast cancer in both the disease free and progressed states was assumed to occur at a rate consistent with the age and gender adjusted rate of the wider population, informed by the ONS's estimates of mortality, which are adjusted to exclude deaths due to breast cancer. [17, 18] An estimate of median life expectancy following disease recurrence is extracted from the study by Chang[19] and re-estimated as a fixed annual probability to inform post metastases mortality, the lower and upper confidence interval from Chang were used to estimate the SE to inform the PSA.

Health related quality of life (HRQoL) outcomes

Estimates to inform the HRQoL of all states in the model are estimated through the combination of two sources. Estimates of the HRQoL of 'cured' patients (i.e. those who had been disease free for 10 years after surgery) are informed by age and gender adjusted population norms.[20] All other states in the Markov model draw from the study by Lidgren,[21] which estimates HRQoL scores in different states of breast cancer using the EQ-5D-3L measure. All HRQoL values were defined as gamma distributions for the PSA.[22]

Non Drug Acquisition Costs

In addition to the short term costs drawn directly from the chemotherapy cost analysis, two further categories of costs are considered: the chemotherapy related adverse events, and the long term costs associated with each of the Markov states. All parameter estimates are presented in Table 1.

The cost of chemotherapy related adverse events are estimated from Paulden (subject to 2012 exchange rate from Canadian dollars as well as inflation),[14] incorporating the cost of treating 11 common adverse events. Paulden is additionally the source of the cost of fatal chemotherapy toxicity. All adverse events are assumed to occur within the first year after treatment. The SEs required to inform the PSA are not reported in Paulden for the adverse event and toxicity costs, as a result the assumption is made that the proportional relationship between the mean and SE observed in the long term costs (presented in the next paragraph) is the same as for these short term costs (a proportion of 0.25).

The long term costs associated with membership of the different states modelled is informed by two sources. The cost to the NHS of providing care for disease free patients reflects the recommendations of NICE that patients should be followed up with annual mammographies,[23] coupled with the argument made by Campbell that disease free patient would be expected to attend two oncology clinics a year.[15] The cost of caring for disease free patients is assumed to be fixed.

All other long term costs are informed by the study by Karnon,[24] which estimated the healthcare costs for the treatment of breast cancer recurrent events. Estimated costs for local, contralateral, and distant recurrence are weighted by their incidence in the Karnon study to estimate a weighted average annual cost for recurrence. To reflect the high initial costs of responding to disease metastases, the model discriminates between the costs to the NHS in the first year post metastases, and all subsequent years. The Karnon study is additionally used to inform the cost of terminal care.

[Table 1 here]

Results

Chemotherapy cost analysis

The short term costs associated with the two arms of the analysis are presented in Table 2, broken down into the acquisition and provision of chemotherapy alone and the impact of additionally incorporating the cost of EndoPredict. Further details of the treatment regimens recommended at each stage of the decision and the costing approach are provided in the Supplementary Appendix.

The results show that EndoPredict led to a small but not statistically significant increase in the mean per patient cost of acquisition and provision of chemotherapy to the NHS (£149, $p=0.4366$). This

increase resulted from an insignificant decrease in the cost per cycle (£1 less for the EndoPredict arm, £982 compared to £983) but an increase in the number of cycles prescribed (0.15 cycles more with EndoPredict, 4.52 compared to 4.68).

Despite the number of patients receiving chemotherapy in the two arms of the analysis being similar (61 for standard decision criteria only and 62 for EndoPredict plus standard criteria) the mix of patients is very different. 28 patients who, using standard criteria only, would have had no chemotherapy had their treatment plan changed to receive chemotherapy with EndoPredict, similarly 27 patients had their treatment changed from chemotherapy to no chemotherapy.

Table 2 additionally shows that when the cost of providing EndoPredict to all 149 patients, is included in the analysis, the expected cost difference becomes statistically significant (£1,593, $p=0.0004$).

[Table 2 here]

Cost-effectiveness Analysis

The probabilistic results of the long term cost-effectiveness analysis are presented in Table 3. They show that the use of EndoPredict to inform clinical decision making is expected to be associated with higher average discounted costs (£1,482 more), more life-years (0.13) and more QALYs (0.06). As a result the base case analysis suggests that, at a cost-effectiveness threshold of £20,000 per QALY, the use of EndoPredict is not cost effective, with an incremental cost-effectiveness ratio (ICER) of £26,836/QALY.

[Table 3 here]

The implications of the use of EndoPredict over time can be conceptualised by plotting the incremental cumulative net monetary benefit (NMB), as shown in Figure 2. The NMB is a combined measure of the incremental cost and QALYs associated with an intervention, estimated using the formula:

$$\text{NMB} = (\text{QALYs} \times \text{cost-effectiveness threshold}) - \text{costs}$$

Further details regarding the use and interpretation of the incremental cumulative NMB curve are published elsewhere.[25] The figure shows that the initially high incremental cost associated with EndoPredict, due to both the cost of the test and additional chemotherapy, is slowly recouped as the long term health benefits that result from the improved decision making are realised. The figure shows that, assuming a cost-effectiveness threshold of £20,000/QALY, the incremental NMB never

become positive. However, with a threshold of £30,000/QALY after 27 years sufficient benefits have been recouped to make the use of EndoPredict cost-effective given the base-case assumptions.

[Figure 2 here]

The uncertainty around the base-case result can be characterised through the PSA, which allows for the estimation of the probability that each decision is cost-effective at different thresholds, and thus test the parametric uncertainty. This is achieved through the combination of the estimated point probabilities in Table 3, the 'cloud' of PSA iteration results in Figure 3, and the cost-acceptability curves in Figure 4. These show that the high level of uncertainty in several parameters permeates into the final result, and that while in only a very small number of iterations (0.07%) EndoPredict was found to dominate the standard tool arm, such that it was both cheaper and more effective at a threshold of £20,000/QALY, it was associated with the larger probability of being cost effective (39.6%). A small proportion of iterations resulted in EndoPredict being associated with fewer QALYs (16%).

[Figures 3 and 4 here]

Furthermore, it is possible to quantify the scale of the likely consequences of an incorrect decision through the use of value of information methodology,[22] which combines the likelihood of an incorrect decision at given cost-effectiveness threshold, the cost and QALY consequences if the decision is wrong, and the size of the population expected to be treated. An estimate of the effective population was estimated using incidence data from CRUK[26] and Macmillan,[27] along with an estimate of the proportion of patients who would receive an intermediate risk score using standard criteria from Paulden,[14] and thus be eligible for use of EndoPredict, giving a per annum incident population of 7,114. Coupled with the assumption of a 10 year technology horizon the model estimates the consequence of decision uncertainty at a threshold of £20,000/QALY to be £23.4m (equivalent to 1,171 QALYs).

A number of one way sensitivity analyses were also conducted, adjusting the key parameters by $\pm 20\%$ to explore the impact on the ICER. The results are produced in a tornado diagram in the Supplementary Appendix, showing that the result was found to be sensitive to changes in the progression rate, age and the discount rate as was expected a priori. However, these scenarios are purely illustrative as the changes are arbitrary, but reflect the areas of key sensitivity in the model.

Test of the 'deviation factor'

One of the strengths of this analysis and the trial on which it is based is the incorporation of the reality that even if an EndoPredict test is conducted patients (and their doctors) may still decide

against the treatment decision recommended by EndoPredict. This can be seen in Table 1 where despite 17 patients (23% of the EPclin high patients) having a high EPclin score they chose to not have any chemotherapy, and 5 (7% of the EPclin low patients) with a low EPclin score chose to have chemotherapy. These events are referred to here as the 'deviation factor', and the scale of deviation that might cause EndoPredict to no longer be cost-effective can be tested in the mathematical model through one and two way scenario analysis. Using a threshold analysis we can estimate the level of 'deviation', or compliance of the final treatment choice with the recommended clinical guidance, at which the results of this cost-effectiveness analysis would be different.

At a cost-effectiveness threshold of £20,000/QALY, as used in the base-case analysis, no level of deviation from the EndoPredict treatment recommendation was found to change the result that the use of EndoPredict is not cost-effective.

However, at a threshold of £30,000/QALY, where EndoPredict would be cost-effective a one way sensitivity analysis suggests that if the proportion of EPclin high patients deviating from the recommended treatment reaches 34% OR the proportion of EPclin low reaches 10% (assuming the other remains as the base case rate) EndoPredict would no longer be cost-effective at a threshold of £30,000/QALY. A two way analysis, maintaining the proportional relationship between the two deviation rates suggests that if the proportion of EPclin high deviating reached 29% AND the EPclin low reached 8% EndoPredict would no longer be cost-effective. A simpler way to report the results of this analysis is that if the total proportion of patients deviating from the recommended treatment rose by 25% from those seen in the trial, given the assumptions of the base case analysis, EndoPredict would no longer be cost effective.

Discussion

This analysis of the EndoPredict trial found that the use of EndoPredict to aid chemotherapy decision making for patients with an initial intermediate risk score using standard decision criteria is not expected to be cost-effective compared to no additional decision tool at a cost effectiveness threshold of £20,000/QALY. However, with an ICER of £26,836/QALY it would be considered cost-effective at the upper bound of the NICE cost-effectiveness threshold, and as such falls within the grey area created by NICE's soft threshold where consideration of broader factors including decision uncertainty is vital.

The evaluation demonstrated that while EndoPredict was more expensive in the short term, due to both the upfront cost of the test and increased chemotherapy costs, the ability of the test to affect a more optimal allocation of chemotherapy, with 55 of 149 patients having a change of treatment

decision, resulted in long term health gains. However, while the base-case analysis results in an ICER under the upper £30,000/QALY threshold conventionally used[11] the small scale and lack of follow up of the informative trial resulted in a large level of uncertainty around this conclusion, shown by the high level of decision uncertainty (39.6% at £20,000/QALY). As a result the consequence of decision uncertainty, an estimate of the population health implications should the findings of this analysis be found to be incorrect as further evidence emerges, are high (estimated at £23.4m, equivalent to 1,171 QALYs). While recognised to be hard to set against a reference standard,[28] these findings demonstrate the importance of further research in this area, whether or not EndoPredict is recommended for routine use in the NHS in this population.

In addition to the evaluation's robust quantification of the intrinsic uncertainty of the decision, it is strengthened by its ability to capture and reflect the frequency with which the treatment decision deviated from the recommended action estimated from EndoPredict. Such factors are highly relevant in real world clinical application, as the final, patient based, treatment decision is likely to take into account factors beyond simple clinical and cost-effectiveness, and thus must be reflected.

The available evidence has, however, led to a number of weaknesses of the analysis. Primarily, the failure of the model to reflect the range of comparators to EndoPredict detailed in the recent NICE Guidance and Medtech Innovation Briefings.[3-5] Attempts were made to identify relevant evidence with which to synthesise the findings of the EndoPredict trial, however, no studies were found relevant to the decision problem and the population. While the NICE Guidance[3] reports some elements of their evaluation of some EndoPredict comparators (primarily Oncotype DX and ICH4), the lack of sufficient detail with which to compare their analytical approach with that presented here, makes any direct comparison potentially misleading, demonstrated by the significant difference in the mean lifetime cost and QALY of a patents on current practice across the two studies. However, it is believed that current NHS standard practice remains the use of non-gene informed prognostic tools, and as such the failure of this analysis to incorporate comparators remains relevant to the current decision problem. Our analysis is focussed on the NHS due to the setting of the trial and availability of relevant evidence, however, we believe our findings are applicable to other economies with developed healthcare services. However, some international health technology agencies have different approaches to defining an appropriate cost-effectiveness threshold, as a result while the core findings may apply the decision maker's conclusion regarding cost-effectiveness may differ.

Other weaknesses include the presentation of the EPclin categorisation of patients as a binary high or low risk, while this is representative of its current use, ideally an analysis would be conducted that

reflected its continuous nature, determining the most cost-effective threshold for the provision of chemotherapy. Similarly, while the various forms of chemotherapy prescribed in the trial are incorporated into the costing, there was insufficient evidence available in the literature relating to comparative effectiveness to reflect the potential impact of these difference regimens on long-term health outcomes, necessitating a simple chemotherapy or no chemotherapy decision problem. The use of a small, single armed trial to inform the clinical role of EndoPredict also risks introducing unobserved bias to the analysis which may not be fully incorporated in the sensitivity analyses conducted.

Furthermore, the use of relatively old evidence to inform our analysis, including post-metastatic survival estimates from a 2003 potentially biases the results, in this case overestimating the benefits of early diagnosis. The incorporation of newer analysis published since this analysis was conducted would be expected to increase the cost-effectiveness of EndoPredict as the importance of early diagnosis is reduced with increase effectiveness of treatment for metastatic cancer.[29, 30]

Additionally, the use of standard treatment decision making by the treating oncologist and patient as one of the treatment arms risks introducing uncertainty as it was difficult within the scope of the trial to determine what factors were considered most important or the use of additional tools such as PREDICT and Adjuvant! Online. However, this is considered to be indicative of current practice within the NHS.

As with any analysis, especially those such as this which rely on relatively small trial evidence with short follow-up, assumptions are required to consider the long-term cost-effectiveness, such as assuming the consistency of the trial population with that studied in Blank et al. However, it is our view that given such decisions must be made by decision makers it is often necessary to make such assumptions in light of limited evidence. Such results should be used to highlight areas of further research.

By using a three state Markov model our analysis represents a simpler form than published elsewhere, for example by Hall et al.[31] While the analysis presented here was conducted in 2015, prior to the publication of these more detailed analyses, and a more detailed natural history model may provide additional capacity to identify benefits and costs of treatments, we do not believe the use of a three state model can be definitively correlated with a bias when estimating the cost-effectiveness of EndoPredict.

While a number of studies have considered the role of gene informed prognostic tools for all Oestrogen Receptor +ve and HER-2 negative post-surgery breast cancer patients, only the NICE

Diagnostic Guidance[3] has considered in detail the subgroup relevant to this study, those who additionally have an intermediate risk of recurrence using a non-gene informed tool. However, the NICE Guidance did not consider the use of EndoPredict due to its market release after the analysis. As a result, this study represents the first of its kind and is expected to be highly informative to subsequent evaluations by NICE and other health technology assessment bodies. Finally, we reflect that tools such as EndoPredict and its competitors do not exist on a dichotomous scale but as continuous risk scores which are used by clinicians and decision makers to inform relatively binary treatment decisions. Therefore, we believe that future research is needed on the implications of the interpretation of the continuous risk scores on not only clinical outcomes but also cost-effective outcomes.

References

1. Office for National Statistics, *Cancer Registration Statistics, England, 2012*. ONS: Newport, Statistical Bulletin, 2014.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), *Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials*. The Lancet, 2005. **365**(9472): p. 1687-1717.
3. NICE, *DG10: Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat*. NICE: London, 2013.
4. NICE, *MIB44: EndoPredict gene expression profiling assay for assessing risk of breast cancer recurrence*. NICE: London, 2015.
5. NICE, *MIB27: The Prosigna gene expression profiling assay for assessing longterm risk of breast cancer recurrence*. NICE: London, 2015.
6. NICE, *Tumour profiling tests to guide adjuvant chemotherapy decisions in people with breast cancer*. NICE: London, forthcoming
7. Bloomfield, D.J., et al., *Patient/oncologist decisions about adjuvant chemotherapy in ER+ve, HER2-ve early breast cancer following endopredict testing*. Journal of Clinical Oncology, 2017. **35**(15_suppl): p. e12002-e12002.
8. Filipits, M., et al., *A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors*. Clinical Cancer Research, 2011. **17**(18): p. 6012-6020.
9. Blank, P., et al., *Cost-Effectiveness Analysis of Prognostic Gene Expression Signature-Based Stratification of Early Breast Cancer Patients*. Pharmacoeconomics, 2015. **33**(2): p. 179-190.
10. Kronenwett, R., et al., *Decentral gene expression analysis: analytical validation of the Endopredict genomic multianalyte breast cancer prognosis test*. BMC Cancer, 2012. **12**(1): p. 456.
11. NICE, *PMG9: Guide to the methods of technology appraisal 2013*. NICE: London, 2013.
12. Curtis, L. and A. Burns, *Unit Costs of Health and Social Care 2015*. Personal Social Services Research Unit, University of Kent, Canterbury., 2015.
13. Joint Formulary Committee, *British National Formulary*. ed. London: BMJ Group and Pharmaceutical Press, 2015.
14. Paulden, M., et al., *Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer*. Value in Health, 2013. **16**(5): p. 729-739.
15. Campbell, H.E., et al., *The cost-effectiveness of adjuvant chemotherapy for early breast cancer: A comparison of no chemotherapy and first, second, and third generation regimens for patients with differing prognoses*. European Journal of Cancer, 2011. **47**(17): p. 2517-2530.
16. Mark Mitchell, Baurzhan Muftakhidinov, and T. Winchen, *Engauge Digitizer Software*. Webpage: <http://markummitchell.github.io/engauge-digitizer>, Last Accessed: April 27, 2017.
17. Office for National Statistics, *National Life Tables, 2008-2010*. ONS: Newport, 2011.
18. Office for National Statistics, *England and Wales Breast Cancer Mortality*. ONS: Newport, 2005.
19. Chang, J., et al., *Survival of patients with metastatic breast carcinoma*. Cancer, 2003. **97**(3): p. 545-553.
20. Kind P, H.G., Macran S. , *UK Population Norms for EQ-5D* York: Centre for Health Economics, University of York, 1999. **Discussion Paper 172**.
21. Lidgren, M., et al., *Health related quality of life in different states of breast cancer*. Quality of Life Research, 2007. **16**(6): p. 1073-1081.
22. Michael F. Drummond, et al., *Methods for the economic evaluation of health care programmes: Fourth Edition*. Oxford Medical Publications, 2015.

23. NICE, *CG80: Early and locally advanced breast cancer: diagnosis and treatment*. NICE: London, 2009.
24. Karnon, J., et al., *Health care costs for the treatment of breast cancer recurrent events: estimates from a UK-based patient-level analysis*. British Journal of Cancer, 2007. **97**(4): p. 479-485.
25. Claxton, K., et al., *A Comprehensive Algorithm for Approval of Health Technologies With, Without, or Only in Research: The Key Principles for Informing Coverage Decisions*. Value in Health, 2016. **19**(6): p. 885-891.
26. Cancer Research UK, *Breast Cancer Incidence Statistics*.
<http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive>. **Last Accessed: 27/04/2017.**
27. Macmillan Cancer Research, *Types of Breast Cancer*.
<http://www.macmillan.org.uk/information-and-support/breast-cancer/understanding-cancer/types-of-breast-cancer.html>. **Last Accessed: 27/04/2017.**
28. Hettle R, C.M., Hinde S, Hodgson R, Jones-Diette J, Woolacott N, Palmer S, *The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal*. Health Technol Assess, 2017. **21**(7).
29. Gobbini, E., et al., *Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort*. Eur J Cancer, 2018. **96**: p. 17-24.
30. Prat, A., et al., *Prognostic Value of Intrinsic Subtypes in Hormone Receptor-Positive Metastatic Breast Cancer Treated With Letrozole With or Without Lapatinib*. JAMA Oncol, 2016. **2**(10): p. 1287-1294.
31. Hall, P.S., et al., *Value of Information Analysis of Multiparameter Tests for Chemotherapy in Early Breast Cancer: The OPTIMA Prelim Trial*. Value in Health, 2017. **20**(10): p. 1311-1318.

Figure 1: schematic showing model structure

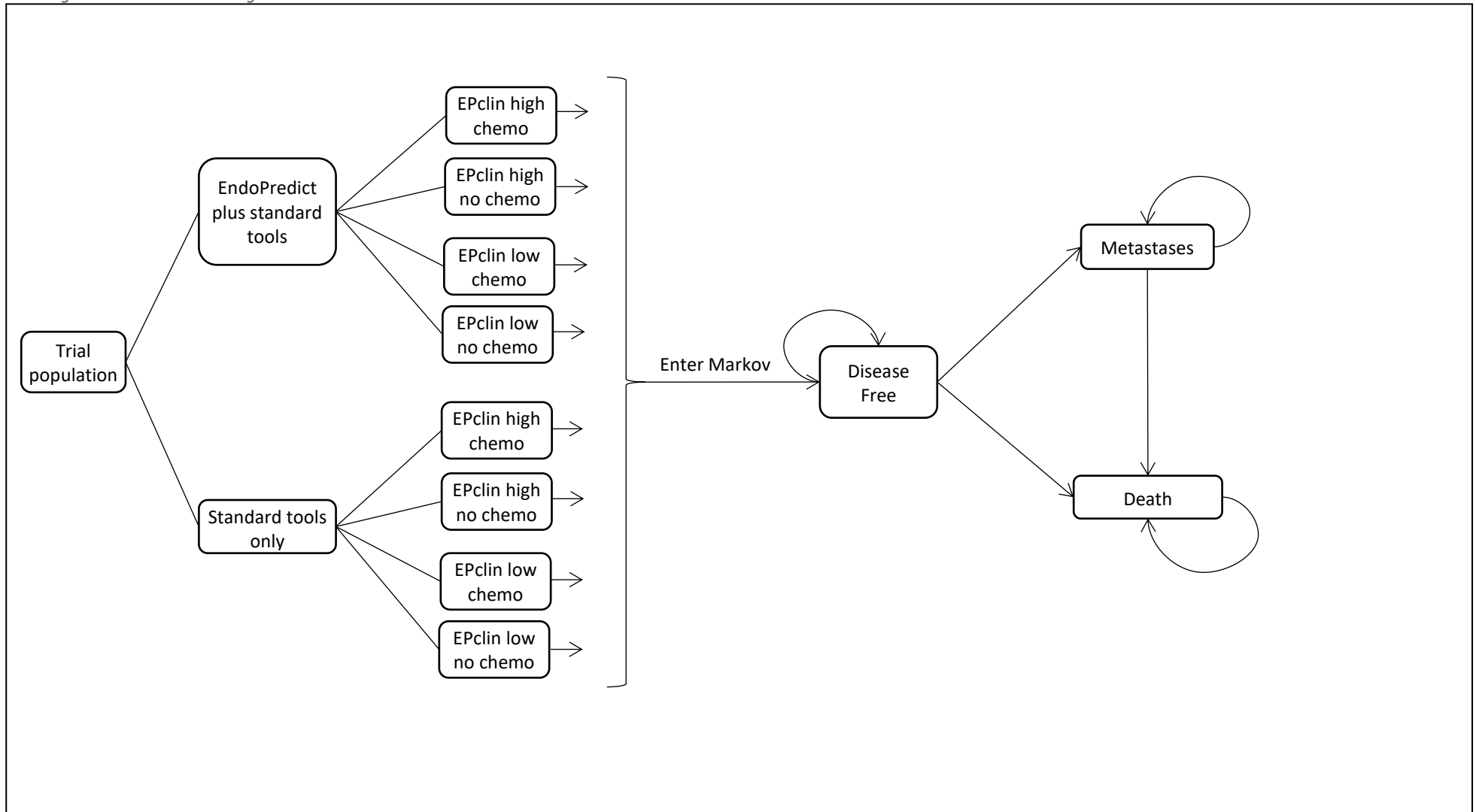


Figure 2: Incremental NMB over time, at cost-effectiveness thresholds of £20,000/QALY and £30,000/QALY, (discounted)

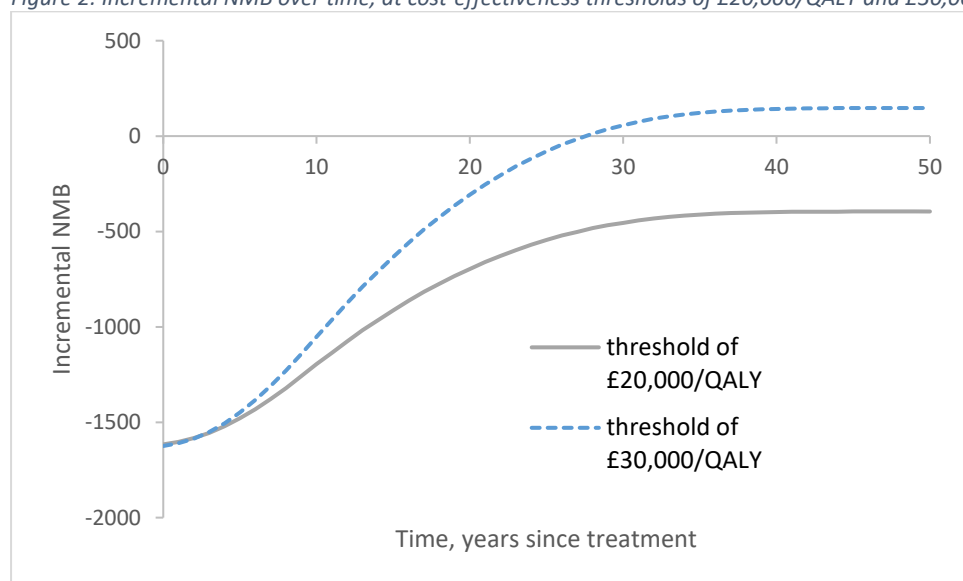


Figure 3: Cost-effectiveness scatter plot across all PSA iterations, plus cost-effectiveness threshold line (£20,000/QALY) and mean incremental cost and QALY point

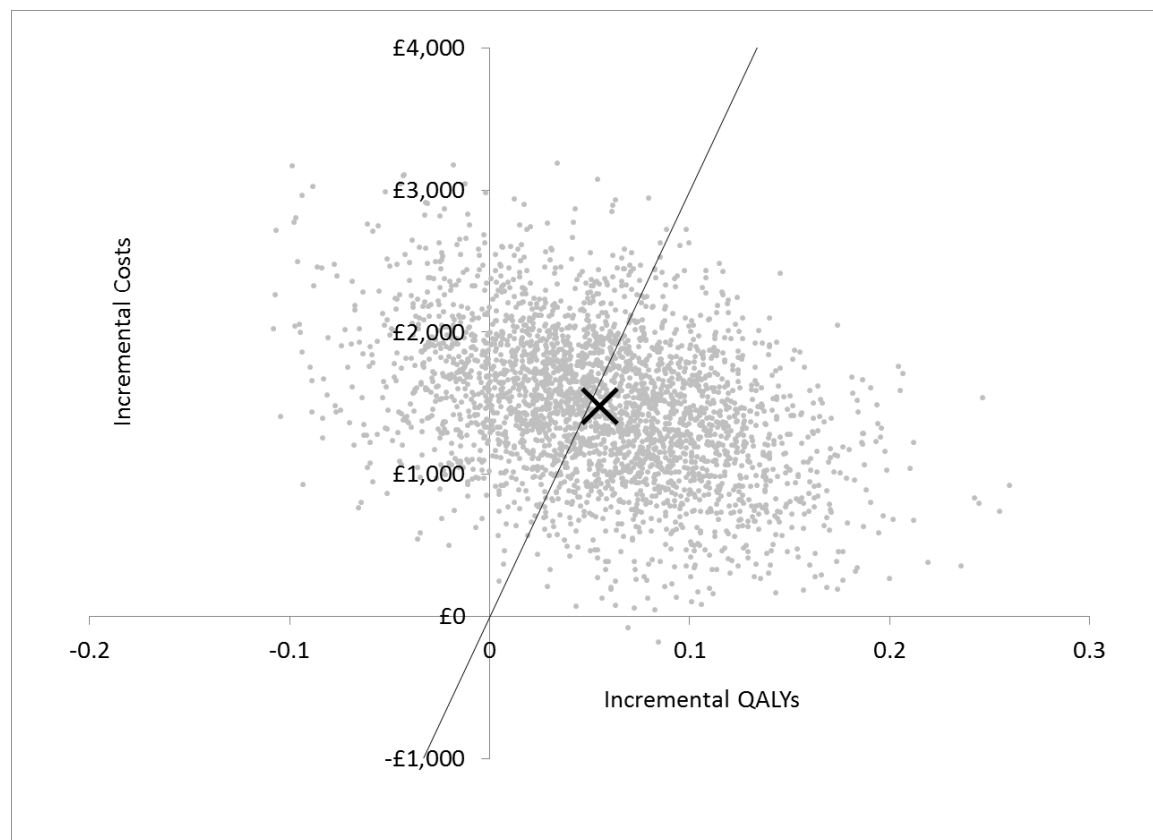
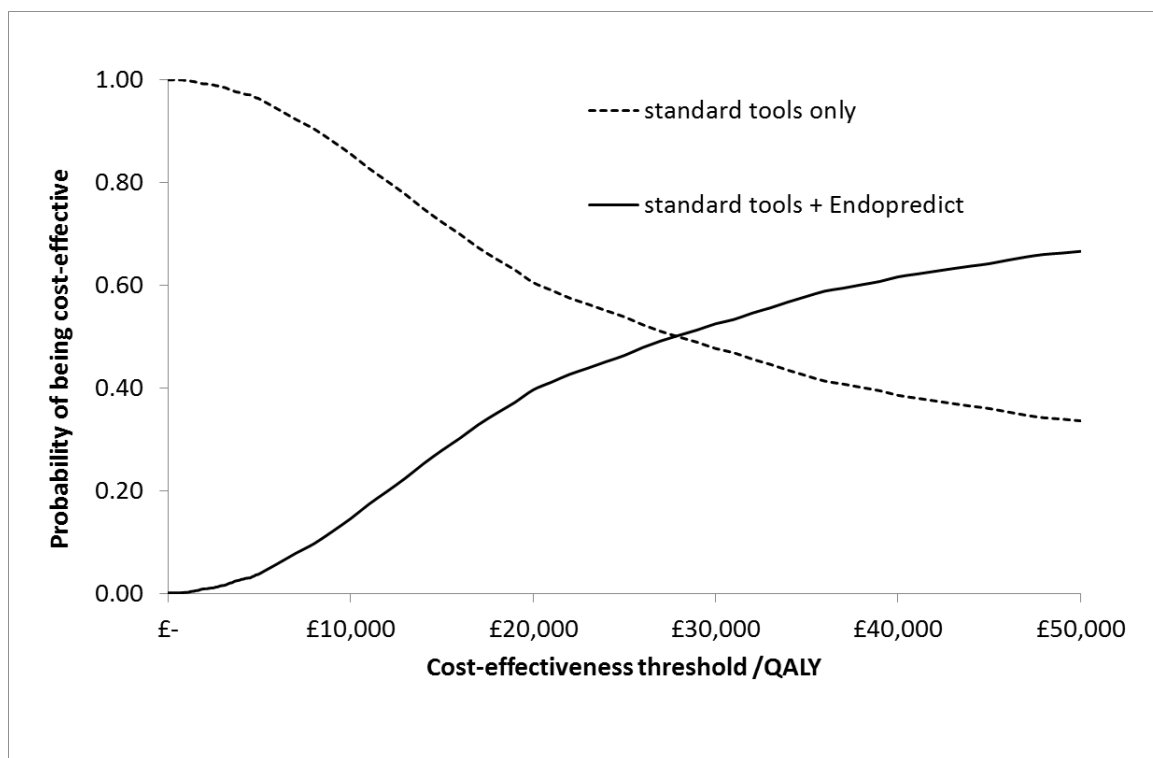


Figure 4: Cost-effectiveness acceptability curves



Supplementary Appendix

Figure 1A: Histogram of nodal involvement at initial visit

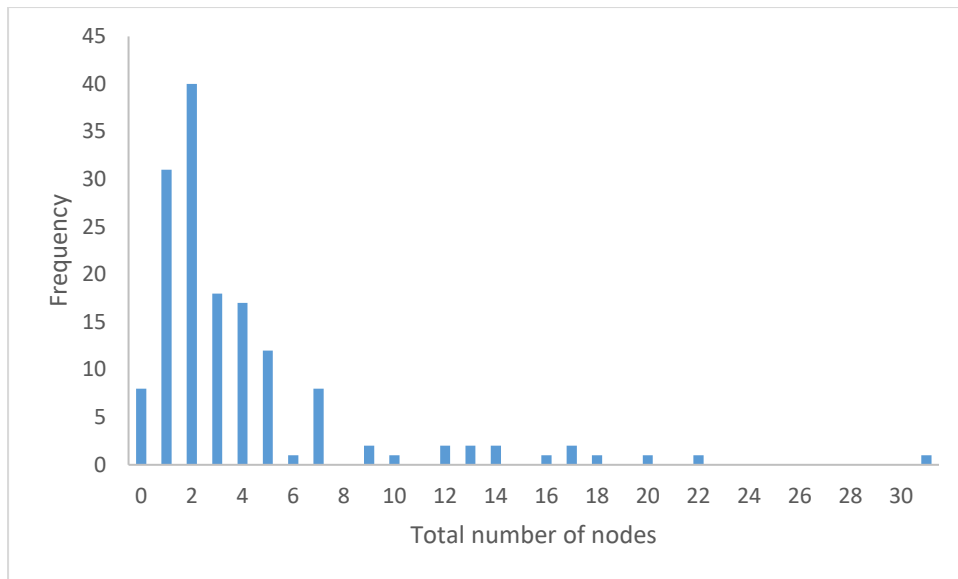


Table 1A: Details of the chemotherapy regimen recommended at first and second decision

	First decision		Second decision	
	Frequency	percentage	Frequency	percentage
adriamycin (doxorubicin) plus cyclophosphamide	31	20.8	30	20.1
epirubicin plus cyclophosphamide	4	2.7	5	3.4
epirubicin plus cyclophosphamide plus docetaxel	0	0.0	1	0.7
epirubicin plus cyclophosphamide plus paclitaxel	0	0.0	2	1.3
Endocrine only	88	59.1	87	58.4
FEC	8	5.4	9	6.0
FEC-T	7	4.7	4	2.7
Docetaxel plus cyclophosphamide	11	7.4	11	7.4

Figure 2A: Tornado plot of one way sensitivity analyses

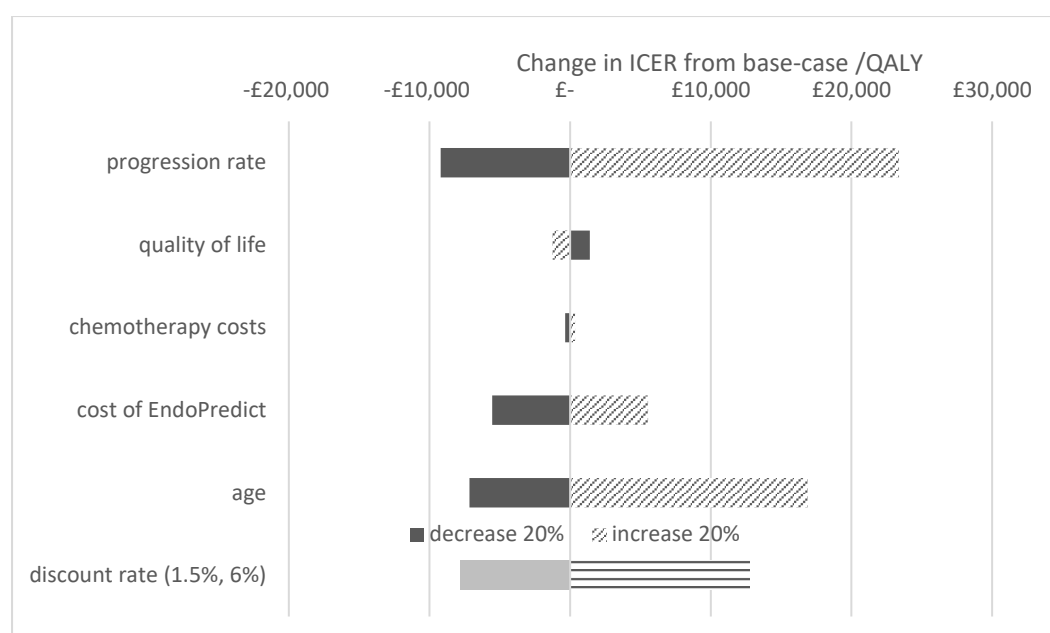


Table 2A: Systematic search strategy used to identify relevant previous analyses

Number of searches	Location of key word	Key word
#1	MeSH descriptor	breast cancer
#2	MeSH descriptor	breast cancer prognosis
#3	MeSH descriptor	breast tumours
#4	MeSH descriptor	breast tumors
#5	MeSH descriptor	estrogen receptor
#6	MeSH descriptor	oestrogen receptor
#7	MeSH descriptor	Endopredict
#8	MeSH descriptor	Oncotype Dx
#9	Title/Abstract	[Clinical validation] and [Endopredict]
#10	MeSH descriptor	GEICAM 9906 trial
#11	MeSH descriptor	ABCSG 8 trial
#12	Title/Abstract	[Endopredict] and [cost effectiveness]
#13	Title/Abstract	[Endopredict] and [economic analysis]
#14	Title/Abstract	[Endopredict] and [economic evaluation]
#15	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 or #9
#16	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 or #10

#17	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 or #11
#18	MeSH descriptor	[multigene prognostic tool]
#19	MeSH descriptor	[molecular predictor]
#20	MeSH descriptor	[prognostic classification]
#21	MeSH descriptor	[gene expression analysis]
#22	MeSH descriptor	[21 gene RT-PCR assay]
#23	Title/Abstract	(multigene prognostic tool and cost effectiveness) or prognostic tool and economic analysis) or prognostic tool and economic evaluation)
#24	Title/Abstract	(molecular predictor and cost effectiveness) or (molecular predictor and economic analysis) or (molecular predictor and economic evaluation)
#25	Title/Abstract	(prognostic classification and cost effectiveness) or (prognostic classification and economic analysis) or (prognostic classification and economic evaluation)
#26	Title/Abstract	(gene expression analysis and cost effectiveness) or (gene expression analysis and economic analysis) or (gene expression analysis and economic evaluation)
#27	Title/Abstract	(21 gene RT-PCR assay and cost effectiveness) or (21 gene RT-PCR assay and economic analysis) or (21 gene RT-PCR assay and economic evaluation)
#28	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 and #20
#29	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 and #21
#30	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 and #22
#31	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 and #23
#32	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 and #24
#33	Title/Abstract	[distant recurrence] and [cost effectiveness]
#34	Title/Abstract	[Chemotherapy] and [decision making]

#35	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 or #30
#36	All Fields (Combined search)	#1 or #2 or #3 or #4 or #5 or #6 or #31

Table 1: Parameter estimates

Parameter (distribution)			Value	SE or Alpha/Beta	Source
EndoPredict and treatment classification, number of patients (Dirichlet)	Standard clinical decision only	EPclin high chemo	32 (21.5%)	N/A estimates for PSA defined by Dirichlet	Results drawn directly from trial[24]
		EPclin high no chemo	42 (28.2%)		
		EPclin low chemo	29 (19.5%)		
		EPclin low no chemo	46 (30.9%)		
	Standard clinical decision and EndoPredict	EPclin high chemo	57 (38.3%)		
		EPclin high no chemo	17 (11.4%)		
		EPclin low chemo	5 (3.4%)		
		EPclin low no chemo	70 (47.0%)		
Transition probabilities	Hazard ratio for risk of disease metastases for those on chemotherapy (normal)		0.69	0.04	[8]
	Probability of chemo toxicity related mortality (beta)		3.71×10^{-3}	Alpha – 28 Beta - 7540	[14]
	DF to recurrence, 0 to 10 years, exponential shape estimate (normal)	EPclin high	0.9996	1.43×10^{-5}	[8]
		EPclin low	0.9984	3.07×10^{-5}	
	DF to recurrence, 10 years plus		0	N/A	Assumption
	Recurrence to death (normal)		0.327	0.0263	[18]
Utilities	Year 1 no chemo (gamma)		0.744	Alpha – 118 Beta – 6.28×10^{-3}	[20]
	Year 1 chemo (gamma)		0.62	Alpha – 167 Beta – 3.71×10^{-3}	
	Year 2-10 metastases-free (gamma)		0.779	Alpha – 2140 Beta – 3.64×10^{-3}	
	Year 10+ no chemo (gamma)		Age adjusted population norms		[19]
	Recurrence no chemo (gamma)		0.648	Alpha – 102 Beta – 6.38×10^{-3}	[20]

	Recurrence chemo (gamma)		0.692	Alpha – 404 Beta – 1.71 $\times 10^{-3}$	
Costs	Cost of Endopredict (fixed price)		£1,500	N/A	[4]
	Chemo costs	Acquisition costs and number of cycles	Informed by trial analysis reported in Results		
		Non-acquisition costs, per cycle (fixed)	£139.39	N/A	[13]
	Mean cost of treating chemo adverse events		£736.73	Alpha – 16.7 Beta – 44.2	[13]
	Cost of fatal chemo toxicity (gamma)		£22,485.20	Alpha – 16.7 Beta – 1350	[13]
	Cost of care disease free patients (fixed)	0 to 5 years after surgery	£328.48	N/A, assumed fixed	[14, 22, 25]
		5+ years	£0	N/A	
	Cost of care regressed patients (gamma)	1 st year post regression	£13,329.16	Alpha – 177 Beta – 75.4	[23]
		2+ years	£4,079.51	Alpha – 403 Beta – 10.1	
	Cost of terminal care for all patients except chemo toxicity (gamma)		£4,491.99	Alpha – 79.0 Beta – 56.9	

Table 2: Results of cost-minimisation analysis

	Mean standard tools only cost (SD)	Mean EndoPredict and standard tools decision cost (SD)	Total cost difference (per patient average, p value that difference is significant)
Cost of the acquisition and delivery of chemotherapy per treated patient	£4,687 (5,074) over 61 patients	£4,836 (5,261) over 62 patients	+£13,924 (£149, p=0.4366)
Total short term cost (chemotherapy costs plus cost of EndoPredict to all follow-up)	£1,919 (3,972)	£3,512 (4,138)	+£237,357 (£1,593, p=0.0004)

Table 3: Results of the cost-effectiveness analysis, estimates are per patient

Screening decision	Expected costs (discounted)	Expected Life Years (undiscounted) Expected LYs	Expected QALYs (discounted)	ICER (cost per QALY)	Probability of being cost-effective at a threshold of...	
					£20,000/QALY	£30,000/QALY
standard tools only	£7,228	26.57	12.65	N/A	60.4%	47.6%

EndoPredict and standard tools	£8,710	<u>26.70</u>	12.70	£26,836/QALY	39.6%	52.4%
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